Safety Data Sheet

Vincristine sulfate

Division of Safety
National Institutes
of Health

WARNING!

THIS COMPOUND IS TOXIC ON INGESTION, PARENTERAL INJECTION, AND ON CONTACT WITH SKIN AND EYES. IT IS TERATOGENIC AND EMBRYOTOXIC.

HANDLE WITH EXTREME CARE. AVOID SKIN AND EYE CONTACT AND BREATHING OF DUST. ON EXPOSURE, WASH SKIN IMMEDIATELY WITH SOAP AND WATER. IRRIGATE EYES.

IF INHALED, MOVE TO CLEAN AIR. CALL PHYSICIAN.

DO NOT TAKE INTERNALLY.

A. Background

Vincristine is an alkaloid isolated from the leaves, bark or stem of the Madagascar periwinkle Catharanthus roseus G. Don (formerly called Vinca rosea Linn). It is a dimer of an indole (catharanthine) and a dihydroindole (indoline, vindoline) moiety. The sulfate (VCR), the form in which it is used in medical practice, is a white to slightly yellow hygroscopic crystalline compound, soluble in water and methanol. It is highly toxic in all mammalian species tested (parenteral and oral LD50 in the mg/kg range) and embryotoxic and teratogenic. Exposure of skin and eyes may produce vesication. Its major use is as an antineoplastic against acute leukemias and certain lymphomas and neuroblastomas. In low doses (which are nontoxic and have no antitumor effects per se) it also increases the effectiveness of other antineoplastics (e.g., 5-fluorouracil, actinomycin D). Its dose-limiting effects are neuromuscular in nature due to demyelination of peripheral nerves. Its mode of action is an inhibition of mitotic processes due to strong binding

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to the protein tubulin in mitotic spindles, with formation of cytoplasmic inclusion bodies ("microtubule crystals") leading to inhibition of biosynthesis of DNA, RNA and protein.

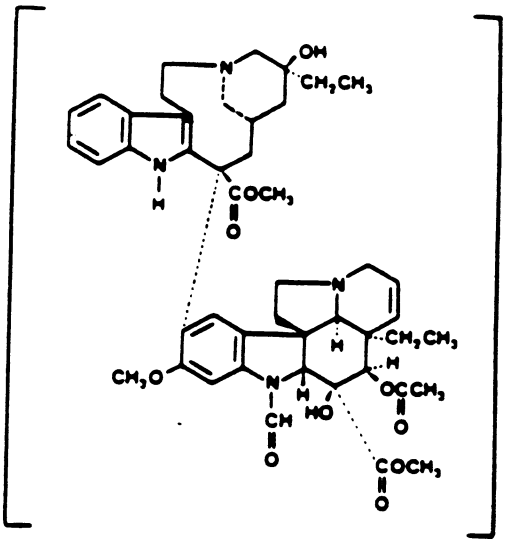
General reviews include Burns (1972), Creasey (1975), IARC (1981).

B. Chemical and Physical Data

1. Chemical Abstract No.: 57-22-7 for the free base; 2068-78-2 f the sulfate.

2. Synonyms: Leurocristine sulfate (1:1);[A] vincaleukoblastine, 22-oxo-sulfate (1:1);[B] LCR; VCR; VCR sulfate. Trade names: NS 67574; Oncovin; Vincrisul; NCI-CO4864; Kyocristine.

3. Chemical structure and molecular weight:



Catharanthine moiety

Vindoline moiety

free base: $C_{46}H_{56}N_4O_{10}$; M.W. 825
sulfate: $C_{46}H_{56}N_4O_{10}.H_2SO_4$; M.W. 923

4. Density: No data.

5. Absorption spectroscopy: Ultraviolet maxima at 221, 255 and 29 nm; infrared and NMR spectral data have been tabulated (Burns, 1972).

[A]Chemical Abstracts name, used for listing in 7th and 8th Decennial Index.

[B]Chemical Abstracts name, used for listing in 9th Decennial Index and subsequently.

6. Volatility: No data. VCR may be regarded as essentially nonvolatile.

7. Solubility: VCR is soluble in water (1 in 2), ethanol (1 in 600), chloroform (1 in 30) and methanol; insoluble in ether (IARC, 1981).

8. Description: White to slightly yellow odorless crystalline or amorphous powder. Very hygroscopic. pK_as: 5.0, 7.4.

9. Boiling point: No data; melting point range: 273-281°C when recrystallized from ethanol with loss of solvent at 210-232°C.

10. Stability: Dry VCR is heat-stable in the absence of atmospheric oxygen; decomposition is 2% in sealed ampoules in an inert atmosphere in 16 hours at 100°C but 50% in air. Aqueous solutions are heat-stable at their normal pH of 4.5 but decomposition occurs at pH 2 (Burns, 1972). Since the free base is stated to be unstable, the same probably applies to alkaline solutions of VCR. VCR, like other indole compounds, is probably susceptible to ultraviolet radiation; while there are no quantitative data on the subject, it is recommended that tissue preparations for analytical purposes be carried out under fluorescent light (without an ultraviolet component) or in the dark (Owellen et al., 1981). It should also be noted that VCR is strongly adsorbed by plastic materials such as dialysis tubing (El Dareer et al., 1977) and containers (Benvenuto et al., 1981) as well as by cellulose filters used in intravenous administration devices (Butler et al., 1980).

11. Chemical reactivity: The two ring structures of VCR are subject to the usual reactions such as reduction or acylation of free OH groups, deacylation of acetyl groups, oxidation or reduction of the aldehyde group, substitution of the secondary amino group, etc. Such reactions have been used in synthesis of other congeners of the Vinca alkaloids. The effects of some of these reactions on biological activity have been described (Creasey, 1975; Sieber et al., 1976).

12. Flash point: No data.

13. Autoignition temperature: No data.

14. Explosive limits in air: No data.

Fire, Explosion and Reactivity Hazards

1. VCR is likely to be inactivated under conditions of fire. Because of its vesicant action it is recommended that fire-fighting personnel wear protective clothing and face masks.

2. Flammability is likely to be low.

3. Conditions contributing to instability are exposure to acid or alkali, oxidants, elevated temperatures, or ultraviolet light.

4. Hazardous decomposition products under conditions of fire are nitrogen and sulfur oxides (Sax, 1984).

Operational Procedures

The NIH Guidelines for the Laboratory Use of Chemical Carcinogens describe operational practices to be followed when potentially carcinogenic chemicals are used in NIH laboratories. The Guidelines should be consulted to identify the proper use conditions required and specific controls to be implemented during normal and complex operations or manipulations involving VCR.

Aqueous VCR solutions penetrate various glove materials (Slevin et al., 1984). This factor should be taken into account when handling VCR.

1. Chemical inactivation: Validated methods have been reported (Castegnaro et al., 1985).

2. Decontamination: Turn off equipment that could be affected by VCR or the materials used for cleanup. If more than 1 g has been spilled or if there is any uncertainty regarding the procedures to be followed for decontamination, call the NIH Fire Department (dial 116) for assistance. For details of procedures, see Castegnaro et al. (1985).

3. Disposal: It may be possible to decontaminate waste streams containing VCR before disposal. For details, see Castegnaro et al. (1985). No waste streams containing VCR shall be disposed of in sinks or general refuse. Surplus VCR or chemical waste streams contaminated with VCR shall be handled as hazardous chemical waste and disposed of in accordance with the NIH chemical waste disposal system. Nonchemical waste (e.g., animal carcasses and bedding) containing VCR shall be handled and packaged for incineration in accordance with the NIH medical-pathological waste disposal system. Potentially infectious waste (e.g., tissue cultures) containing VCR shall be disinfected by heat using a standard autoclave treatment and packaged for incineration, as above. Burnable waste (e.g., absorbent bench top liners) minimally contaminated with VCR shall be handled as potentially infectious waste and packaged for incineration, as above. Absorbent materials (e.g., associated with spill cleanup) grossly contaminated shall be handled in accordance with the chemical waste disposal system. Radioactive waste containing VCR shall be handled in accordance with the NIH radioactive waste disposal system.

4. Storage: For information on storage stability see B10. Solid VCR may be stored at room temperature in sealed ampoules with inert atmosphere in the dark.

E. Monitoring and Measurement Procedures including Direct Field Measurements and Sampling for Subsequent Laboratory Analysis.

1. Sampling: No data.

2. Analysis:

a. Introductory notes.

(1) Analytical procedures prior to 1971 have been reviewe by Burns (1972).

(2) In general, analytical methods developed for VCR are also applicable to vinblastine sulfate, and vice versa. Therefore, all methods developed for either compound are quoted below.

b. Sample extraction and preparation: It is important that tissue extractions be carried out at acid pH since structural changes and partial destruction of the Vinca alkaloids may occur at alkaline pH. A method for extraction with 95% ethanol at pH 4.9 has been described (Houghton et al., 1983).

c. Analysis: The two principal methods are based on either bioassay or radioimmunoassay. Both have advantages and disadvantages. Bioassay is the less sensitive of these procedures (lowest detectable concentration is 0.01 µg/ml plasma or 0.1 µg/g tissue) and measures both intact alkaloid and active metabolites, being based on mitotic arrest (Dixon et al., 1969; Aoshima and Sakurai, 1973; Kipp and Barendsen, 1981). None of these reports mentions the presence or absence of crossreaction with, or interference by, other anti-neoplastics which may be present when they are used concomitantly in clinical practice. Radioimmunoassay (RIA) likewise does not distinguish between the alkaloid and its deacetyl derivative which is an active metabolite of vinblastine and probably also of VCR (Owellen et al., 1977).[A] Several such procedures have been described (Owellen et al., 1977; Teale et al., 1977; Langone et al., 1979; Sethi et al., 1980; Owellen et al., 1981). The sensitivity is of the order of 4 ng VCR/ml.

[A]Since all RIA methods depend on the use of tritiated VCR, the production and radiopurity of this compound is of some importance. Usually VCR is tritiated by the Wilzbach procedure in which VCR is exposed to tritium vapor. This results mainly in labelling of the ring structure but also produces ill-defined radioactive impurities (Beer and Richards, 1964; Owellen and Hartke, 1975). A more specific method of preparation has been described by Castle et al. (1976).

Most authors quote absence of interference by non-Vinca alkaloid antineoplastics. It is noteworthy that the procedure described by Langone et al. (1977) is reported to yield antibodies which are 200 times more sensitive for VCR than for vinblastine. Because of the cost of radiolabelled antigen and of measuring equipment, Hacker et al. (1984) have developed an enzyme-linked immunoabsorbent assay (ELISA) which is based on conjugation of vinblastine with alkaline phosphatase, capable of detecting 5 pg of VCR or vinblastine. For measurement of possible metabolites, Castle and Mead (1978) have applied high-pressure liquid chromatography.

Biological Effects (Animal and Human)

1. Absorption: VCR is absorbed and produces biological effects on parenteral (intravenous, the usual clinical method, and intraperitoneal) injection and on ingestion. It acts as a vesicant and may produce contact dermatitis as a result of handling or by extravasation due to needle slipping during treatment; however, it is not known whether systemic toxic effects are produced by this route.

2. Distribution and Pharmacokinetics: Intraperitoneally injected VCR in mice and rats produces a peak serum level after 15 minutes followed by rapid disappearence (El Dareer et al., 1977). Intravenous VCR is cleared from plasma relatively rapidly in all species tested; this clearance has been described as either biphasic for rat, dog and monkey ($t_{1/2}$ 6-15 and 75-190 minutes; Castle et al., 1976; El Dareer et al., 1977) or triphasic for man ($t_{1/2}$ 0.85, 7.4 and 164 min; Bender et al., 1977). This is followed by marked accumulation in all tissues except the brain, with highest amounts (dog, monkey) in pancreas, spleen, kidney, lung and liver.

   Plasma disappearance curves indicate a two compartment system for man (Owellen et al., 1977; van den Berg et al., 1982). Other pharmacokinetic data have been published for rhesus monkeys (Sethi et al., 1984).

3. Metabolism and Excretion: The metabolism of VCR is not well understood, mainly due to analytical difficulties related to the low tolerated dosages and the instability of VCR in analytical systems. Metabolites do occur (as evidenced by differential extractions) but none has been identified to date. In mice, such metabolites after intraperitoneal injection of VCR increase in amount in serum for 30 minutes and stay at a high level for 3 hours. Urinary excretion in 48 hours was 22% in the form of unchanged VCR and 19% as metabolites. In feces, the respective figures were 18 and 19% (El Dareer et al., 1977). In other mammalian species on intravenous injection, the major route of excretion is via the bile, mainly in the form of unchanged VCR (Castle et al., 1976; Castle and Mead, 1978). In man, likewise, 12 and 69% of the tritium label of VCR is excreted in urine and

feces, respectively, within 72 hours after administration of which 46 and 40% were in the form of metabolites (Bender et al., 1977). Since the "metabolites" show an ultraviolet spectrum identical with that of VCR, it is concluded that metabolism involves the side chain rather than the dimeric ring structure of VCR.

Toxic Effects: The acute LD50 of VCR in the mouse is in the range of 2-5 mg/kg by either the intravenous or intraperitoneal route; the rat is slightly more sensitive, showing an intravenous LD50 of 1-1.3 mg/kg. Oral LD50 in the monkey is 2-4 mg/kg. When given in five daily doses intravenously to mice the LD50 was 1 mg/kg/day, indicating a cumulative effect (Adamson et al., 1965; Todd et al., 1976; Houchens et al., 1977; Meeks et al., 1981). The maximum tolerated dose in man is 25 mg/kg (Gout et al., 1978).

The toxic effects in man and animals have been reviewed (DeConti and Creasey, 1975; Goodman and Gilman, 1985) and contrasted with those of vinblastine (Johnson, 1968; Gout et al., 1978). The main (dose-limiting) effect of VCR is peripheral neurotoxicity, with limb weakness or paralysis due to demyelination (Adamson et al., 1965). Other effects are leukopenia and thrombocytopenia, diarrhea, vomiting, anorexia and dyspnea. Alopecia in man is also a common occurrence.

On intradermal injection at doses as small as 1% of the therapeutic dose VCR produces soft tissue necrosis in the guinea pig (Barr et al., 1981) and mouse (Dorr and Alberts, 1985).

The mechanism of toxic and antineoplastic action is cell damage by mitotic interphase-metaphase arrest (Mujagic et al., 1983; Cho et al., 1983). VCR binds strongly to tubulin, a protein constituent of mitotic spindles, with formation of cytoplasmic inclusion bodies ("microtubule crystals") (Owellen et al., 1974). While VCR may form complexes with cytosols from normal tissues also, these are unstable whereas complexes formed with tumor tissues are extremely stable (Houghton et al., 1985) which may explain the differential effect. Binding to tubulin results in inhibition of DNA and RNA and hence protein synthesis.

Carcinogenic effects: The literature has been summarized (IARC, 1981). No evidence of carcinogenicity of VCR in animals has been reported, and where carcinogenicity in humans has been claimed this has been invariably in patients under treatment with a combination of VCR with other antineoplastics, some of which were recognized carcinogens.

Mutagenic and teratogenic effects: VCR is not mutagenic in the Ames test (Seino et al., 1978; Pak et al., 1979) and against Drosophila (Todd et al., 1983). However, it is strongly

embryo-toxic and teratogenic in monkeys (Courtney and Valemo, 1968), mice (Joneja and Ungthavorn, 1969; Wan et al., 1983) and hamsters (Ferm, 1963).

G. Emergency Treatment and Medical Surveillance

1. Skin and eye exposure: For skin exposure, remove contaminated clothing and wash with soap and water. For eye exposure, irrigate immediately with copious quantities of warm water or boric acid solution.

2. Ingestion: Give milk or sodium bicarbonate solution to reduce gastric irritation.

3. Inhalation: Remove to clean air and avoid further contact.

4. Medical surveillance: Pre-employment and periodic surveillance should include liver and kidney function tests, hematological workup, and cardiovascular examination. It is recommended that personnel with preexisting dermatitis as well as women during the first three months of pregnancy not be exposed to VCR. The treatment of skin dermatitis in animals, which is probably applicable to extravasation during injection or accidental exposure of laboratory workers, has been described (Dorr and Alberts, 1985).

. References

Adamson, R.H., R.L. Dixon, M. Ben, L. Crews, S.B. Shochet, and D.P. Rall. 1965. Some pharmacological properties of vincristine. Arch Int Pharmacodyn Ther 157:299-311.

Aoshima, M. and Y. Sakurai. 1973. A new bioassay method for vincristine in animal tissues. Gann 64:207-209.

Barr, R.D., S.G. Benton, and L.W. Belbeck. 1981. Soft-tissue necrosis induced by extravasated cancer chemotherapeutic agents. J Natl Cancer Inst 66:1129-1136.

Beer, C.T. and J.F. Richards. 1964. The metabolism of Vinca alkaloids. II. The fate of tritiated vinblastine in rats. Lloydia 27:352-360.

Bender, R.A., M.C. Castle, D.A. Margileth, and V.T. Oliverio. 1977. The pharmacokinetics of [^{3}H] vincristine in man. Clin Pharmacol Ther 22:430-438.

Benvenuto, J.A., R.W. Anderson, K. Kerkof, R.G. Smith, and T.L. Loo. 1981. Stability and compatibility of antitumor agents in glass and plastic containers. Am J Hosp Pharm 38:1914-1918.

Burns, J.H. 1972. Vincristine sulfate. in Analytical Profiles of Drug Substances. Vol. 1, pp. 463-480 Florey, K. (ed).

Butler, L.D., J.M. Munson, and P.P. DeLuca. 1980. Effect of in-line filtration on the potency of low-dose drugs. Am J Hosp Pharm 37:935-941.

Castegnaro, M., S.C. Adams, M.-A. Armour, J. Barek, J. Benvenuto, C. Confalonieri, U. Goff, S. Ludeman, D. Reed, E.B. Sansone, and G. Telling, eds. 1985. Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some Antineoplastic Agents. IARC Scientific Publications No. 73. World Health Organization, Geneva, Switzerland.

Castle, M.C., D.A. Margileth, and V.T. Oliverio. 1976. Distribution and excretion of [^{3}H] vincristine in the rat and dog. Cancer Res 36:3684-3689.

Castle, M.C. and J.A.R. Mead. 1978. Investigation of the metabolic fate of tritiated vincristine in the rat by high-pressure liquid chromatography. Biochem Pharmacol 27:37-44.

Cho, E.-S., H.E. Lowndes, and B.D. Goldstein. 1983. Neurotoxicology of vincristine in the cat. Arch Toxicol 52:83-90.

Courtney, K.D. and D.A. Valerio. 1968. Teratology in the Macaca mulatta. Teratology 1:163-172.

Creasey, W.A. 1975. Vinca alkaloids and colchicine. in Antineoplastic and Immunosuppressive Agents, Part II, Ch. 67, pp. 670-694 Sartorelli, A.C. and D.G. Johns (eds). Springer, N.Y.

DeConti, R.C. and W.A. Creasey. 1975. Clinical aspects of the dimeric Catharanthus alkaloids. in The Catharanthus Alkaloids, pp. 237-278 Taylor, W.L. and N.R. Farnsworth (eds). Marcel Dekker, N.Y.

Dixon, G.E., E.A. Dulmadge, L.T. Mulligan, and L.B. Mellett. 1969. Cell culture bioassay for vincristine sulfate in sera from mice, rats, dogs and monkeys. Cancer Res 29:1810-1813.

Dorr, R.T. and D.S. Alberts. 1985. Vinca alkaloid skin toxicity: Antidote and drug disposition studies in the mouse. J Natl Cancer Inst 74:113-120.

El Dareer, S.M., V.M. White, F.P. Chen, L.B. Mellett, and D.L. Hill. 1977. Distribution and metabolism of vincristine in mice, rats, dogs and monkeys. Cancer Treat Rep 61:1269-1277.

Ferm, V.H. 1963. Congenital malformations in hamster embryos after treatment with vinblastine and vincristine. Science 141:426.

Goodman, L.S. and A. Gilman, eds. 1985. The Pharmacological Basis of Therapeutics, 7th ed. pp. 1277-1280, Macmillan, N.Y.

Gout, P.W., L.L. Wijcik, and C.T. Beer. 1978. Differences between vinblastine and vincristine in distribution in the blood of rats and binding by platelets and malignant cells. Eur J Cancer Clin Oncol 14:1167-1178.

Hacker, M.P., J.R. Dank, and W.B. Ershier. 1984. Vinblastine pharmacokinetics measured by a sensitive enzyme-linked immunosorbent assay. Cancer Res 44:478-481.

Houchens, D.P., R.K. Johnson, M.R. Gaston, A. Goldin, and T. Marks. 1977. Toxicity of cancer chemotherapeutic agents in athymic (nude) mice. Cancer Treat Rep 61:103-104.

Houghton, J.A., P.M. Torrance, and J.P. Houghton. 1983. Chromatographic analysis of Vinca alkaloids in human neoplastic tissues and host (mouse) tissues after injection in vivo or after incubation in vitro. Anal Biochem 134:450-454.

Houghton, J.A., L.C. Williams, and J.P. Houghton. 1985. Stability of vincristine complexes in cytosols derived from xenografts of human rhabdosarcoma and normal tissues of the mouse. Cancer Res 45:3761-3767.

IARC, International Agency for Research on Cancer. 1981. Vincristine Sulphate. IARC Monographs 26:365-384.

Johnson, I.S. 1968. Historical background of Vinca alkaloid research and areas of future interest. Cancer Treat Rep 52:455-461.

Joneja, M. and S. Ungthavorn. 1969. Teratogenic effects of vincristine in three lines of mice. Teratology 2:235-240.

Kipp, J.B.A. and G.W. Barendsen. 1981. Pharmacokinetics of vinblastine in rat blood plasma and tumor tissue determined by a biological method using flow cytofluorimetry. Eur J Cancer Clin Oncol 17:867-873.

Langone, J.J., M.R. D'Onofrio, and H. van Vunakis. 1979. Radioimmunoassays for the Vinca alkaloids vinblastine and vincristine. Anal Biochem 95:214-221.

Meeks, R.G., E.P. Denine, L.D. Stout, J.C. Peckham, and A.M. Guarino. 1981. Toxicological evaluation of intravenously-administered vincristine (NSC 67574) in BDF 1 mice. NTIS Report PB82-166141; Chem Abstr 97:84893g.

Mujagic, H., S.-S. Chen, R. Geist, S.J. Occhipinti, B.M. Conger, C.A. Smith, W.H. Schuette, and S.E. Shakney. 1983. Effects of vincristine on cell survival, cell cycle progression, and mitotic accumulation in asynchronously growing sarcoma 180 cells. Cancer Res 43:3591-3597.

Owellen, R.J., D.W. Donigian, C.A. Hartke, R.M. Dickerson, and M.J. Kuhar. 1974. The binding of vinblastine to tubulin and to particulate fractions of human brain. Cancer Res 34:3180-3186.

Owellen, R.J. and C.A. Hartke. 1975. The pharmacokinetics of 4-acetyl tritium vinblastine in two patients. Cancer Res 35:975-980.

Owellen, R.J., M.A. Root, and F.O. Hains. 1977. Pharmacokinetics of vindesine and vincristine in humans. Cancer Res 37:2603-2607.

Owellen, R.J., M. Blair, A. van Tosh, and F.C. Hains. 1981. Determination of tissue concentrations of Vinca alkaloids by radioimmunoassay. Cancer Treat Rep 65:469-475.

Sax, N.I. 1984. Dangerous Properties of Industrial Materials. 6th ed. Van Nostrand Reinhold, N.Y.

Sethi, V.S., S.S. Burton, and D.V. Jackson. 1980. A sensitive radioimmunoassay for vincristine and vinblastine. Cancer Chemother Pharmacol 4:183-187.

Sethi, V.S., P. Surratt, and C.L. Spurr. 1984. Pharmacokinetics of vincristine, vinblastine, and vindesine, in rhesus monkeys. Cancer Chemother Pharmacol 12:31-35.

Sieber, S.M., J.A.R. Mead, and R.H. Adamson. 1976. Pharmacology of anti-tumor agents from higher plants. Cancer Treat Rep 60:1127-1139.

Slevin, M.L., L.M. Ang, A. Johnston, and P. Turner. 1984. The efficiency of protective gloves used in the handling of cytotoxic drugs. Cancer Chemother Pharmacol 12:151-153.

Teale, J.D., J.M. Clough, and V. Marks. 1977. Radioimmunoassay of vinblastine and vincristine. Br J Clin Pharmacol 4:169-172.

Todd, G.C., W.R. Gibson, and D.M. Morton. 1976. Toxicology of vindesine (desacetyl vinblastine amide) in mice, rats and dogs. J Toxicol Environ Health 1:843-850.

Todd, N., J. Clements, P. Zoeller, and M. Phillips. 1983. Absence of mutagenic effect after feeding 4 anti-cancer drugs to Drosophila melanogaster. Mutat Res 120:121-125.

Van den Berg, H.W., Z.R. Desai, R. Wilson, G. Kennedy, J.M. Bridges, and R.G. Shanks. 1982. The pharmacokinetics of vincristine in man: Reduced drug clearance associated with raised serum alkaline phosphatase, and dose-limited elimination. Cancer Chemother Pharmacol 8:215-219.

Wan, Y.-J., T.-C. Wu, and I. Damjanov. 1983. Immediate and delayed effects of vincristine administered during early postimplantation stages of murine embryogenesis. J Exp Zool 227:49-55.